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APPENDIX J

ANTICHOLINERGIC DRUGS AND THE EEG

by

Max Fink, M.D.

This review examines the effects of anticholinergic compounds on the human central nervous system, in relation to their military testing. Such compounds were tested in volunteers to define their role as incapacitating agents for military use. The question presented is whether, as tested, the chemicals are likely to produce adverse health effects or delayed sequelae in the test subjects, or whether it is possible even to predict that likelihood. This review focuses on the data derived from electroencephalography.

The data include protocols of military experiments declassified for this review, reports published in the scientific literature on animals and man, and my own studies. Between 1956 and 1966, experiments were undertaken in my laboratories in New York and St. Louis to define the effects of anticholinergic drugs on brain function and behavior. We sought to determine whether any of the substances had persistent behavioral effects that could be useful in treating the severely mentally ill (1-7).

Atropine and scopolamine (hyoscine) are prototypic anticholinergic compounds. Their effects are principally antimuscarinic. Compounds usually classified with these prototypes are those used in the treatment of parkinsonism--such as procyclidine (Kemadrin), benztropine mesylate (Cogentin), and trihexyphenidyl (Artane)--and such medicinals as glycopyrrolate (Robinol) and methantheline (Banthine). Such experimental anticholinergic compounds as Ditrane, JB-329, JB-336, and WIN 2299 are included in the same class. In some studies, particularly EEG studies in patients, the tricyclic antidepressants imipramine and amitriptyline have been shown to have atropine-like properties.

Electroencephalography developed from studies published in 1929. In the early studies, changes were assessed by visual inspection of ink-written records. These have since been replaced by electronic and, lately, digital computer methods of quantitative analysis. These methods provide excellent assessments of minimal changes in brain function in man. Unfortunately, the military reports are limited to inspection.

LITERATURE REVIEW

The effects of anticholinergic drugs on brain function have been studied extensively. CNS effects in man are defined principally on the basis of self-reports, observer evaluations,

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neuropsychologic tests, and physiologic measures. Of these, the EEG, especially in its present quantitative form, is a sensitive index of changes in CNS activity, with particular relevance to human performance and states of vigilance (8,9).

Anticholinergic drugs have well defined effects on the EEG, accompanied by measurable behavioral effects. In most drug studies, EEG patterns correlate well with behavioral changes. Studies of atropine in animals, however, elicited reports that their EEG showed increased amplitudes and lowering of frequencies at times when the animals were apparently restless. Animals examined in halers often exhibited running movements, but their EEG patterns were similar to those seen in deep sleep (10). The apparent purposeful movements associated with "sleep-like" EEG records led some observers to define an "EEG-behavioral dissociation" with anticholinergic drugs (1, 11-15). In studies of psychoactive substances in man, we and others found a close relationship between the changes in EEG patterns and the behavioral effects of drug administration (8). The difference in observations between animals and man led to a symposium in 1966 that summarized the data available to that time (1). The symposium participants concluded that the apparent "dissociation" in EEG and behavior with anticholinergic drugs was limited to observations in animals and was an artefact of the gross nature of the measures used in animal trials, rarely, the inability to assess changes in cognition, vigilance, mood, and affect (which are principal targets of anticholinergic drugs).

Anticholinergic drugs have a characteristic dose-related effect on brain function, and particularly on the resting, alert scalp-recorded EEG (3,4,6,7,16-27).

Low doses, such as 1-2 mg of atropine, are sufficient to induce mild tension, irritability, and anxiety. The subjects are aware of changes in their perception and mood, and they make errors on cognitive tests. At these times, the EEG patterns exhibit an increase in high frequencies and decreases in the mean alpha frequency and in the amplitude of the dominant (alpha) frequencies. These effects may be accompanied by a decrease in heart rate and some minimal effects on salivation and skin conductance (28, 29). With higher doses, such as 10-30 mg, or repeated administrations, the subjects become delirious, showing restlessness, impairment of motor and sensory functions, cognitive defects, illusory sensations, and thought disorder, including hallucinations and delusions. Heart rate is increased, and the peripheral effects of dry mouth and skin, decreased urination, and difficulty in near vision are prominent. The EEG shows an increase in slow waves, a decrease in mean frequency, a decrease in the percent time and amplitudes of alpha activity, and an increase in the high frequencies, which can be seen to be "riding" on the slow waves. There is a direct association between the amount of EEG fast waves with behavioral restlessness and the amount of EEG slow waves with stupor and cognitive defects. At "toxic" doses, patients are in stupor or coma, with rapid heart rate and lowered blood pressure. The EEG demonstrates persistent high-voltage slow waves, with a minimum of alpha and high frequencies.

In epileptic patients, single intramuscular administrations of atropine at up to 2 mg/kg (30) and 1.2 mg of intravenous hyoscine (24) elicited epileptic spike EEG activity. The changes were transient, and the records and behavior of the patients returned to normal within 24 h.

EEG and behavioral effects may be modified by the concurrent administration of other drugs. Thus, atropine (or Ditrane) and chlorpromazine resulted in behavioral stupor that was very deep (allowing surgery without pain responses), accompanied by persistent EEG high-voltage slow waves and decreases in fast waves. When Ditrane and yohimbine or Ditrane and imipramine were given together, restlessness increased, as did the ratio of fast waves to slow waves in the EEG. When patients who exhibited a toxic delirium to Ditrane or atropine were given tetrahydroaminacrin (THA), the stupor was relieved and the EEG showed decreases in both the low and high frequencies (1,7,31).

After acute administration of various compounds, the time for recovery varies with dose--at low doses, the peak effects on parenteral administration are seen in 0.5 h and last for up to 6 h; at high doses, the effects persist for up to 24 h; at toxic doses, there is a return to baseline values the second day after administration. Followup EEG data are limited, the principal data being reports of atropine toxicity. The few statements about EEGs suggest that the effects are gone within a few days of the last exposure (32-37).

In studies of imipramine, some patients developed an acute psychotic reaction. These patients were identified as being young and as exhibiting a "schizophrenic" syndrome--an observation that led to administration of imipramine as a test of "schizophrenia" (2,38).

Although no long-term EEG study of anticholinergic drugs is available, one study of cholinesterase inhibitors may be cited. Duffy *et al.* (39) reported persistent quantitative differences in EEG patterns between workers exposed to the organophosphate compound sarin and a control group of workers in the same plant not so exposed.

MILITARY DATA

The principal military data on EEG studies are in the summaries provided in Case Report Summaries - Anticholinergics, and an addendum provided in a letter by Dr. Frank Marzulli of October 8, 1981. This latter summary included all the useful EEG records cited in the formal protocols of the military studies. No EEG records were found of subjects receiving atropine, scopolamine, EA 3443, or EA 3167. Of the available records, five were related to BZ, two to EA 3580, and one to EA 3834.

The reports stated that the pretreatment records were within normal limits and the postexposure records, taken at various times, were also within normal limits. The records were assessed visually. The reports did not state the conditions of testing, nor is it clear how long after exposure the testing was done.

These records were customary for the time and reflected nonspecific effects that are similar to those reported for many CNS active compounds. The reports did provide neuropsychologic-test

data, however, which indicate that the effects of exposures to the anticholinergic substances on the military volunteers were transient, reverting to baseline values within a few hours or, in a few tests repeated at longer intervals, within a few weeks (40-49). In other studies of the relationship between the changes induced in EEG and in neuropsychologic tests by CNS-active drugs, there was a parallel in the onset and duration of the effects in the different measures. Arguing by analogy, we would anticipate similar reversions to normal for the EEG changes in these volunteers.

Conclusions

In the experiments in which patients and normal volunteers were exposed to single or multiple doses of anticholinergic drugs, a consistent pattern of EEG and behavioral change has been described. In most volunteer studies, doses have been low, exposures usually single, and effects transient. There is no evidence of persistence of behavioral or EEG effects in these experimental trials (50).

In patients who have been given heroic doses of atropine and scopolamine (up to 250 mg) and in whom the doses have often been repeated three times a week for up to 4 mo, there have been few signs of persistent toxicity. The patients have been subjected to periods of coma lasting up to a day. Death has been reported in only one instance. In many patients, the persistent effects have been considered salutary--i.e., the patients have been considered improved in mental state and discharged to the community! In the remainder, they have been reported to be no worse than before treatment. Considering the many hundreds of patients so treated and the continuation of this form of therapy in patients in eastern Europe today, it is unlikely that there is a behavioral syndrome of toxicity.

Focusing exclusively on the anticholinergic properties of the drugs examined in military volunteers, considering the low doses used and the minimal exposures, and aware that heroic doses of anticholinergic drugs (inexplicably) fail to stimulate a defined toxic syndrome, we deduce that the single exposures of doses of anticholinergic drugs used in the volunteers were insufficient to stimulate a persistent toxic syndrome. The data available are sufficient to conclude that, as tested, the chemicals are not likely to produce adverse health effects.

For a more definitive conclusion, a prospective study or a study similar to that reported by Duffy *et al.* (39) in parkinsonism patients or industrial workers exposed to anticholinergics is required.

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APPENDIX K

BIOCHEMICAL ASPECTS OF ANTICHOLINERGIC CHEMICALS

by

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There have been few published studies--an example is that by Jovic and Zupanc (1)--on the biochemical mechanisms associated with quinuclidinyl benzilate (BZ). A major attribute of atropine, scopolamine, and other anticholinergic compounds is their ability to interact with postsynaptic muscarinic binding sites. It is through such an action on smooth muscle that our ideas about BZ and other potent anticholinergics have developed. A property common to all is a high affinity for muscarinic receptor sites ($K_D = 0.05 - 0.1 \times 10^{-9} \text{ M}$). A regional study with [^3H]BZ of binding capacity in hippocampus, frontal cortex, and caudate nucleus of human brain showed (2), small decreases in these areas in Huntington's chorea patients as compared with normal human brain. Atropine and BZ were alike in binding capacity to these sites. Because of the high affinity of BZ for muscarinic receptors, Yamamura and Snyder (3) were first to show its binding to postsynaptic sites, but failed to find evidence of presynaptic sites in the CNS. The suggestion by Polak and Meews (4) that the increased release of acetylcholine in vivo could be accounted for by blockade of "presynaptic" muscarinic receptors therefore requires another explanation.

An early finding by Sacktor (5) is that acetylcholine ($8.6 \times 10^{-5} \text{ M}$) increases phosphatidyl-L-serine, as well as phosphoinositide and phosphatidic acid. In addition, atropine ($1.6 \times 10^{-6} \text{ M}$) and BZ ($7 \times 10^{-5} \text{ M}$) blocked the ACh-stimulated incorporation of ^{32}P into phosphoinositides, but stimulated incorporation of labeled phosphate into phosphatidyl serine. This suggests that, although events related to muscarinic receptor action are blocked by antimuscarinic drugs, other actions may be stimulated. It is known that calcium ions activate phospholipase-C and stimulate the turnover of phospholipids, such as triphosphoinositides, in excitable membranes. Calcium ions have diverse functions in the regulation of cell function. They are required for the release of acetylcholine (6) in neuromuscular transmission and they influence threshold and other attributes of CNS action potentials. It is estimated that intracellular "ionized" calcium is low in neurons (about 10^{-7} M). A small rise in intracellular calcium will produce a sharp rise in K^+ conductance, hyperpolarization, and depression of excitability. The slowed excitation of central neurons by the muscarinic actions of acetylcholine may be countered by anticholinergic drugs and thus account for many of the central effects of BZ in volunteers reported

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by Ketchum (7) and by Sidell (8). Most prominent among these are amnesia, confusion, and disorientation lasting 2 to 6 d. Although the effects of BZ are qualitatively similar to the pharmacologic actions of atropine and scopolamine, the potency and especially the duration of action of BZ are considerably greater. That situation is very likely related to properties other than the binding affinity, which is about the same for all these compounds for the muscarinic receptor ($K_D = 10^{-9}$ M).

The π -bond properties of quinuclidinyl compounds probably account for their "sticking" to tissue constituents for long periods. Experimentally, a 5-mg/kg dose of radiolabeled BZ prevented auditory stimuli for 7-8 d, but labeled drug was hardly detectable in brain after 3 d. Unfortunately, the only thorough study was that by Gosselin *et al.*, (9), on [14 C]atropine, so direct comparisons are difficult. Although atropine abuse with 2,5-dimethoxy-4-ethyl amphetamine (STP) has been reported (10), the number of "bad trips" made its popularity short-lived. The absence of further reports on abuse of atropine-like drugs suggests that their abuse by the volunteers in question does not constitute a long-term problem.

Administration of atropine or scopolamine to animals increases acetylcholine output from the exposed cerebral cortex (11). This has led to the hypothesis of a direct effect on presynaptic muscarinic receptors that regulate ACh release. The finding of release when Ca^{2+} -free Ringer's solution is present (12) led to the suggestion that interneurons are more sensitive to a local decrease in Ca^{2+} ions than the cholinergic nerve endings whose release they modulate. Alternatively, the ability of BZ, Ditran, and other anticholinergic drugs to cause the release of calcium from intraneuronal binding sites (13) could also explain the *in vivo* observations. The role of ionized calcium in the release of ACh in neuromuscular and electroplax preparations is well characterized. It is persuasively argued that, when ACh emerges from a terminal, it has to pass through some sort of "gate" that is a Ca^{2+} -dependent channel; the "gate" is more likely to be open when the terminal is depolarized. The suggestion that control of ACh release is at the level of calcium displacement by BZ is important, because it is the Ca^{2+} -dependent property of "anticholinergic" drugs, and not their antimuscarinic actions, that explains why BZ and Ditran are much more active than atropine centrally. They appear to be equally effective peripherally, when comparisons are based on affinity for muscarinic binding sites.

Calcium ion contents can be regulated by any of the membrane systems that are in contact with the cytosol, e.g., plasma membrane, endoplasmic reticulum, and mitochondrial inner membrane. In brain, mitochondria are in the highest concentration at nerve terminals and represent the major supplier of cellular energy (ATP). Mitochondria can take up Ca^{2+} ions by an energy-requiring process and release free Ca^{2+} in exchange for Na^+ ions. The high capacity of isolated brain mitochondria to transport Ca^{2+} ions has led to the suggestion of a significant role for this organelle in ionic homeostasis. The early observations on energy metabolism demonstrated that Ditran and BZ selectively interfered with the increased energy needs *in vitro* of depolarized cerebral tissue. In contrast, atropine and scopolamine were either without effect or active only at much higher concentration. In the presence of

isolated brain mitochondria, Ditrane (JB339) was shown to interfere with ATP production (13). Calcium retention by brain mitochondria is lost when energy generation (ATP) is interfered with (14). The significance of these and other studies is that BZ and Ditrane are quantitatively different from the less-potent atropine and scopolamine. A selective action on Ca^{2+} channels by BZ and Ditrane on particularly vulnerable neurons would explain the unevenness in the correlation between the receptor-binding properties and behavioral alteration by antimuscarinic compounds in animals and man.

CONCLUSION

Reports of biochemical effects of anticholinergic compounds contain data on animals and may or may not permit extrapolation to man. There is evidence that the actions of quinuclidine derivatives are longer-lasting and the limited metabolic data available suggest that they may be retained in tissues for a longer period. Peripherally, the benzilates are acetylcholine antagonists with high affinity (low KDs). They bind reversibly to muscarinic receptors. Centrally, however, their actions are more complex, and pharmacodynamic and pharmacokinetic properties play an essential role. The available evidence is not entirely convincing that their basis of central action is through postsynaptic muscarinic receptor binding, and their presynaptic role in calcium metabolism must be seriously considered. Without morbidity data, our present biochemical information cannot help to predict long-term effects of exposure to anticholinergic agents.

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APPENDIX L

STRUCTURE-ACTIVITY RELATIONS OF THE CENTRALLY ACTIVE ANTICHOLINERGIC AGENTS

by

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The structure-activity relationships of a large number and variety of anticholinergics have been described in several reviews (1-3), and only the general features will be described here. The main difficulty in comparing chemical structure with psychopharmacologic potency is that unequivocal behavioral measurements of potency are deficient. Although some anticholinergics have been evaluated for their psychotomimetic potency in man (2,4), the comparisons are based largely on a battery of psychopharmacologic measures in animals, including hyperactivity (5), swim maze (6), characteristic exploratory head movements (2), and operant conditioning (7-9). The limitations and reliability of these comparisons have been discussed elsewhere (3), and they do permit generalizations concerning the relative ability of the anticholinergics to produce behavioral disturbances in animals that may reflect psychotogenic potency in man. Structural variations in the heterocyclic amino alcohol result in marked changes in potency; the most potent anticholinergic is 3-quinuclidinyl benzilate, with its rigid conformation (Figure L-1).

With respect to the acid moiety of the anticholinergics, the following structure-activity relationships are found:

As R_1 is increased from methyl to higher alkyls or becomes hydrogen, alkenyl, amino, or aminoalkyl, psychotropic potency diminishes without much effect on peripheral anticholinergic action.

R_2 should be an unsubstituted phenyl group, whereas R_3 must be either a cycloalkyl, alkynyl, thienyl, or unsubstituted phenyl. Alkyl, aryl, halide, or hydroxyl substituents on the phenyl rings abolish central action and diminish anticholinergic potency. R_2 and R_3 can also be replaced by hexahydrofluorenyl (10).

o As "n" is increased beyond 2 or "Y" beyond zero, psychotropic, but not anticholinergic, potency decreases. The position of the ester side chain affects central, but not peripheral action, with the 4-piperidyl ester being most potent, the 3-ester second most and the 2-ester least.

o R_4 must be a hydroxyl group, whereas compounds with hydrogen or an isosteric methyl group are devoid of central action and have diminished anticholinergic action. If R_4 is hydrogen and the hydroxyl group is present on phenyl, central potency is retained.

The duration of the psychotropic action of the various anticholinergics depends both on the type of heterocyclic amino

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group and on R₂ and R₃. The quinuclidinyl and pyrrolidyl amino derivatives tend to be longer-acting than piperidyl, tropanyl, or granatonyl; a cycloalkyl group in R₂ or R₃ prolongs duration. An alkynyl group in R₂ or R₃ decreases duration, whereas increasing chain length or branching of the alkynyl group correspondingly increases duration.

STEREOSPECIFICITY

The anticholinergic glycolate esters of heterocyclic amino alcohols, including scopolamine and related natural alkaloids, exist as optical isomers, resulting from the asymmetric C of both the amino alcohol and acid moiety. Of the two enantiomers of 3-diphenylacetyl quinuclidine, the (-) isomer had 25 times the antispasmodic potency of the (+) isomer; however, the isomers were of equal toxicity, whereas no difference in antispasmodic potency was noted between the two isomers of the quaternary derivative of 3-quinuclidinyl benzilate (11). With respect to their central action, the (+) and (-) enantiomers, which were prepared from the respective quinuclidinols resolved with (+)-camphor-10-sulfonic acid (11), differ markedly in potency (12,13). The (-) isomer was reported to have about 20 times the potency of the (+) isomer in producing ataxia in dogs (12); however, with the use of more elaborate behavioral measurements in cats, the potency difference was in excess of 100-fold (13). It is conceivable that the (+) isomer of 3-quinuclidinyl benzilate is devoid of activity on the central nervous system, and the slight activity observed may be attributed to a 1% contamination by the (-) isomer.

COMPARISON OF ANIMAL AND HUMAN DATA WITH VARIOUS ANTICHOLINERGIC DRUGS

In general, there is good agreement between the relative pharmacologic potency of various anticholinergic psychotomimetic agents in animals and that in humans. The comparison is applicable to both central and peripheral effects of the anticholinergics and to their duration of action. Table L-1 summarizes the data obtained on the Edgewood volunteers who were given a single dose of an anticholinergic agent. Central nervous system (CNS) potency and peripheral antimuscarinic potency are expressed on an arbitrary scale of 0-10, with 10 being the most potent. Most of the agents used were of comparable peripheral antimuscarinic potency, whereas the CNS potency extended over the whole range.

The CNS data in Table L-1 can be summarized as follows. BZ and other quinuclidinyl glycolates containing at least one phenyl and a cycloalkyl group in the acid moiety were the most potent and had the greatest duration of action. The corresponding piperidyl glycolates were one-fifth to one-half as active as the quinuclidinyl esters. It can be concluded from such structure-activity studies, which are based on extensive psychopharmacologic tests in both animals and human volunteers, that BZ is the most representative of the most potent anticholinergics. However, atropine and methylatropine are the most representative of the relatively inactive anticholinergics and could serve as control drugs, particularly because atropine is equipotent, although of shorter duration, to BZ in peripheral anticholinergic effects.

SITES OF ANTICHOLINERGIC ACTION IN BRAIN

Studies have been performed on the regional and cytoplasmic distribution of high-affinity radiolabeled anticholinergics in mammalian brain (14,15). In monkey brain, the regional distribution of [^3H]3-quinuclidinyl benzilate was found to correlate well with other cholinergic measures, such as [^3H]choline uptake, choline acetyltransferase, and acetylcholinesterase (16). By far the highest level of all four parameters was in the putamen and caudate nucleus. The cerebral hemispheres, amygdala, and hippocampus contained about half the concentration of the benzilate, but the other concentrations were small fractions of those in the caudate nucleus. Apart from the caudate nucleus, the correlation between the distribution of the anticholinergics and the measures of cholinergic function was not impressive. By determining the extent to which [^3H]3-quinuclidinyl benzilate binding was diminished by pretreatment of rats with atropine, the degree of specific binding of the anticholinergic can be determined in various brain areas (16). It appears that, although a correlation was found in some brain areas (e.g., the caudate nucleus,) between the distribution of the anticholinergics and other measures of cholinergic action, the binding studies do not permit the conclusion that the drugs' distribution is an accurate reflection of the pattern of muscarinic cholinergic receptors in brain.

The binding of [^3H]-anticholinergics to tissue preparations after lesions are produced in specific brain areas is another means of measuring specific receptors for the anticholinergics. If nerve terminals of the cholinergic afferents to the hippocampus contain muscarinic cholinergic receptors, as suggested by pharmacologic studies (17,18), then lesions in the septal-hippocampal cholinergic tract should reduce the drugs' binding--a conclusion that was experimentally verified (19).

COMPETITION BETWEEN BEHAVIORAL POTENCY AND RECEPTOR AFFINITY

To determine whether the centrally active anticholinergics bind to a physiologic receptor, an attempt was made to correlate inhibition binding constants of the various anticholinergic agents with their psychopharmacologic potency (20). Such a correlation between behavioral and binding data has been attempted with a series of 14 glycolate esters (Figure 2). A linear relation was observed between the behavioral data and the logarithm of the inhibition constants for binding. The behavioral data were taken from previously published accounts and are expressed quantitatively as BDI (behavioral disturbance index, or BDI (21). From the evidence presented in this study, it can be concluded that [^3H]quinuclidinyl benzilate binds to a muscarinic site in brain that is involved in producing the behavioral disturbances elicited by the glycolate esters. This conclusion is based on the low K_d , the saturability and stereospecificity of binding competition studies, and especially the reasonable correlation observed between behavioral and binding data (Figure 2). Although the correlation can be useful in predicting the behavioral potency of new glycolate esters, on the basis of their inhibition constants, there are

notable exceptions, such as atropine, scopolamine, and compound IV. All three drugs had very high affinities for the [³H]quinuclidinyl benzilate binding site, but their behavioral potencies were relatively low. They all contain heterocyclic ring systems other than piperidine or quinuclidine. In a previous study, in an attempt to correlate the behavioral potencies of a series of glycolates with some physical constants, the correlation tended to be excellent for the quinuclidinyl and piperidyl esters, but not for those having other heterocyclic amino rings, such as tropanol and granatanol. However, an excellent correlation was observed between affinity constants and the ability of the anticholinergics to block the acetylcholine-induced contraction of ileum, the correlation being independent of the type of heterocyclic amino ring (20).

A comparison of the receptor binding affinities of the two optical isomers of 3-quinuclidinyl benzilate reveals that the (-) isomer has about 50 times the affinity of the (+) isomer for a synaptic-membrane preparation from rat caudate nucleus (unpublished). It had been reported that the (-) isomer had only 20 times the affinity of the (+) isomer for a neural-membrane preparation from whole rat brain (20). The reasons for the difference may be that caudate nucleus contains a greater concentration of cholinergic receptors and that a purified synaptic membrane preparation was used in the later study. The relative binding affinities of the two isomers however, still had less than the 200:1 potency ratio found in the cat behavioral test (22). A plausible explanation is that the specific neurons associated with the behavioral disturbances of the drugs may have a greater degree of binding stereospecificity than that exhibited by membrane preparations from either whole brain or caudate nucleus.

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TABLE 1

Structure-Activity Data on Anticholinergics in Human Volunteers

<u>Code Name</u>	<u>Dose µg/kg</u>	<u>Duration of Effect, h</u>	<u>Potency^a Peripheral</u>	<u>CNS</u>	<u>No. Subjects</u>
BZ	5-8	48-96	10	10	354
22,608	1-2	48-72	10	10	21
EA 3167	3-4	48-120	10	10	24
301,060	3-5	48-120	10	9	29
CS 27349	7-8	6-24	10	5	50
302,282	7-14	6-12	10	4	8
EA 3580	4-37	12-48	8	3	136
EA 3443	4-60	24-48	8	3	101
302,196	22-54	4-10	8	4	56
Scopolamine	4-16	6-24	10	5	637
302,537	4-6	6-24	10	4	18
Ditran	100	12-24	10	3	12
EA 3834	3-24	12-24	9	4	171
302,668	13-18	12-48	8	8	39
Atropine	1-70	12-24	10	1	602
Benactyzine	100	6-24	4	1	17
Methylscopolamine	1-30	6-30	5	0	66
Methyl atropine	2-20	6-48	8	0	15
302,368	3-4	6-24	10	1	10
Atropine+benactyzine	(100+20)	4-10	10	1	5

^aPotency is expressed in terms of peripheral (mydriasis, dryness of mouth, etc.) and central nervous system (CNS) effects. The latter involve confusion, hallucinations, memory loss, and delirium. Drugs are evaluated relative to BZ.

Figure F-1 Chemical structure of various heterocyclic amino esters of benzoic acid. I = 3-quinuclidinyl, II = N-methyl-4-piperidyl, III = N-methyl-3-piperidyl, IV = N-methyl-3-pyrrolidyl, V = N-methyl-N-methyl-2,3-piperidienyl, VI = 1,2,2,6-tetramethylpiperidyl, VII = N-methyl-3-tropanyl, VIII = N-methyl-3-granatonyl, IX = 1-pyrrolizidinyl, X = 1,2,2,6,6-pentamethyl-3-piperidyl. R = benzilate. Psychotomimetic potency decreases from I to X.

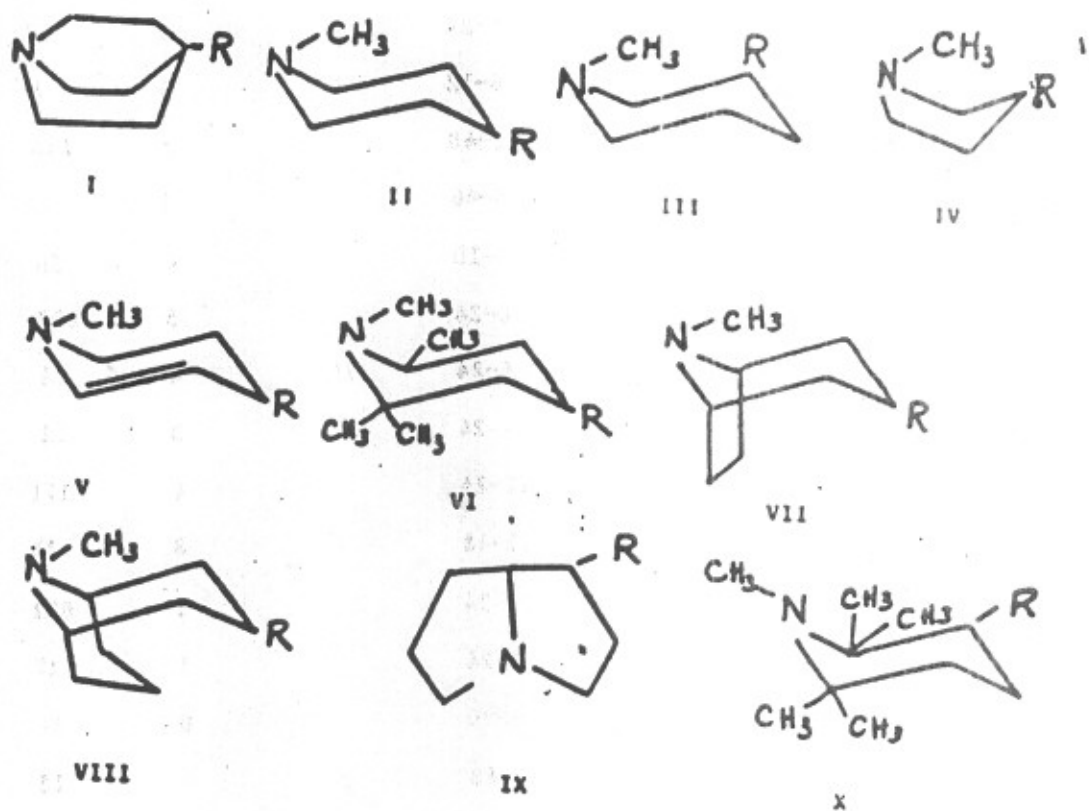


Figure F-2 Correlation of binding affinity of various centrally active anticholinergics to their behavioral disturbance index (BDI). Binding affinity is measured by K_i , the drug concentration producing 50% inhibition of [^3H] quinuclidinyl benzilate binding to brain-membrane preparations. BDI = composite index of behavioral measurements in various animals as a measure of psychotropic potency. Data adapted from Baumgold *et al.* (20).

